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37 C.F.R. §1.8

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Steven L. Highlander

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
KUFER *et al.*

Serial No.: 09/403,107

Filed: October 14, 1999

For: NOVEL METHOD FOR THE PRODUCTION OF ANTIHUMAN ANTIGEN RECEPTORS AND USES THEREOF

Group Art Unit: 1646

Examiner: Gerald R. Ewoldt

Atty. Dkt. No.: DEBE:017US/SLH

INVENTOR'S DECLARATION UNDER 37 C.F.R. §1.132 OF PETER KUFER

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Peter Kufer; do declare that:

1. I am the Peter Kufer named as inventor on the above-captioned application. I reside at Am Kapellenacker 13, 85368 Moosburg, Germany. I am a citizen of Germany.

2. I understand that the examiner for the above-captioned application is arguing that claims 18 and 19 are anticipated by Hoess *et al.* Previously, applicants have argued that the

Hoess *et al.* reference does not teach an antibody that binds 17-1A (synonymous with EGP-2) displayed on the surface of a cell, pointing to the later published de Kruif *et al.* reference as validating this statement. The examiner argues that the de Kruif *et al.* reference does not disclose that the anti-17-1A antibodies described are so limited.

3. As a co-author of the Hoess *et al.* abstract, I am very familiar with the human 17-1A-specific antibody fragments described therein. Despite the title of the abstract - "Generation of human antibodies that selectively recognize diseased cells overexpressing surface bound antigens" - the antibodies mentioned were only reactive with recombinant 17-1A (EpCAM), and failed to bind human 17-1A ***as expressed on the surface of cells, i.e., native 17-1A***. Admittedly, the title and content of the abstract are somewhat misleading as they suggest that both human anti-LeY and human anti-17-1A antibodies were generated recognizing cells over-expressing surface bound antigens. However, this was in fact the case for human anti-LeY only, whereas the human anti-17-1A antibodies did not recognize their antigen in its cell-bound but only in its ***recombinant*** form. This phenomenon, *i.e.*, that antibodies or fragments thereof isolated from combinatorial antibody libraries bind to recombinant antigen, but do ***not*** bind to antigens (over)expressed on the surface of cells, was well known before and well-documented by de Kruif *et al.* (1995) (copy thereof submitted recently). This position is further corroborated by lines 1 to 10 from bottom of the abstract. The relevant passage reads as follows: "To create multivalent antibodies displaying high affinities for cell surface antigens, scFv's can be fused .... The scFv4 recognizes specifically cancer cells overexpressing LeY compared to ...." No equivalent antibody construct recognizing

specifically cancer cells over-expressing 17-1A antigen could be obtained, however. Consequently, the abstract does not report on such antibody constructs. To summarize, Hoess *et al.* did not generate antibodies recognizing cells expressing surface bound human 17-1A, although we were able to isolate antibodies with anti-LeY specificity recognizing cells overexpressing on their surface said antigen.

4. I further understand that the examiner for the above-captioned application is arguing that claims 18-19, 28-31, 38, 39, 53-55, 65 and 67 are obvious over U.S. Patent 6,150,584 ("the '584 patent"), in view of Gottlinger *et al.* It has been argued by applicants that, due to the difficulty of making antibodies to ubiquitous self antigens, there was a lack of predictability that human anti-17-1A antibodies could be created at the time of the present invention. My understanding is that now, the examiner argues that the methods of the '584 patent do not depend on a specific type of antigen, such as a ubiquitous self antigen and, therefore, human 17-1A antigen would be expected to elicit an immune response in the human-Ig transgenic mice, such that human anti-human 17-1A specific antibodies should be produced in the human-Ig transgenic mice used in the procedure set out in the '584 patent. I respectfully disagree.

5. Human antibodies recognizing the human 17-1A antigen, as expressed on the surface of cells, could not, at the time the present application was filed, be obtained without undue burden from the human-Ig transgenic mice used in the procedure set out in the '584 patent. The reason is that the transgenic mice of the '584 patent carry a human Ig-repertoire – the same repertoire that is found in humans – and this is evolutionarily biased

against conserved self antigens such as 17-1A. Thus, the same under-representation of self specificities like 17-1A will appear in the transgenic mice of the '584 patent, just as in a real human Ig-repertoire that is evolutionarily biased to avoid such specificities.

6. As evidence of the rarity of anti-human 17-1A specificities, even today there is still no report in the literature on human antibodies against this antigen from human Ig-transgenic mice, although human antibodies against many other less ubiquitous human antigens have been successfully generated using the '584 patent's methods. This was evidenced by searches in the Medline database and in the HCAPLUS database using STN (online scientific and technical information service). The combination of search terms related to transgenic mice/xenomice and various synonyms for the 17-1A antigen did not reveal any publications related to human anti-human 17-1A specific antibodies produced in human-Ig transgenic mice.

7. I hereby declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

01/21/2004
Date

Peter Kufer, Ph.D.